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10/009,581

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EXAMINER

JAGOE, DONNA A

ART UNIT

PAPER NUMBER

1614

MAIL DATE

DELIVERY MODE

01/11/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/009,581

Applicant(s)

CIVAN ET AL.

Examiner

Donna Jagoe

Art Unit

1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 November 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 94-110, 112, 113, 115 and 116 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 94-110, 112, 113, 115 and 116 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 2, 2007 has been entered.

Claims 94-110, 112, 113, 115 and 116 are pending in this application.

Applicants' arguments filed November 2, 2007 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 101 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In particular, "precursor prostaglandins" (present claim 101) is a concept that was not present in the specification as originally filed. Applicants are advised that the issue here is not whether particular instance of a prostaglandin precursor, but rather whether the concept of other prostaglandin precursors other than latanoprost" was present in the specification as originally filed.

The specification as originally filed contains the following disclosures concerning a prostaglandin inhibitor:

(i) "another new type of drug, precursor prostaglandin compounds (e.g., latanoprost) are also in current use". (page 3, lines 27-28).

The above disclosure, however, does not provide adequate support for any prostaglandin precursor. Prostaglandin precursors include essential fatty acids, such as arachidonic acid, linoleic acid, eicosapentanoic acid and dihomogammalinoleic acid. There does not seem to adequate support in the specification for any of these prostaglandin precursors.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words,

structures, figures, diagrams and formula that fully set forth the claimed invention.

Lockwood v. American Airlines, Inc., 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The Examiner is guided in his opinion that Applicant has not adequately described the presently claimed subject matter by the MPEP at § 2163 - 2163.05. In particular, while Applicant's specification as originally filed contained a specific reference to latanoprost as being one example of a prostaglandin precursor but such does not entitle Applicants to now claim all prostaglandin precursors because such represents a subgenus that was not previously set forth or one that would have been immediately envisaged by one skilled in the art from the specification as originally filed. "A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996)"(emphasis added), see MPEP § 2163(I)(A). Also, "See also *In re Smith*. 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) ('Whatever may be the viability of an inductive-deductive approach to arriving at a claimed subgenus, it cannot be said that such a subgenus is necessarily described by a genus encompassing it and a species upon which it reads.' (emphasis added)).", see MPEP § 2163.05(II).

Considering the teachings provided in the specification as originally filed, the Examiner finds that Applicants have failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set for the claimed

invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicants had possession of the concept of a "precursor prostaglandin".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 94-96, 102 and 105-107 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Cherksey U.S. Patent No. 4,950,591.

Cherksey teaches amiloride is an agent that selectively blocks ion transport and interacts with a Sodium Hydrogen Exchange inhibitor at high concentrations (column 1, lines 21-27). Amiloride and derivatives are capable of regulating membrane transport, cellular volume or cellular pressure disorders (column 2, lines 5-10). The amiloride derivatives are useful when applied topically for the treatment of glaucoma (column 3, line 66 to column 4, line 3 and column 5, lines 42-47).

Claims 94 and 102-105 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Drug Facts and Comparisons (1994).

Page 6 of Applicant's instant specification identifies beta-blockers as NHE inhibitors (see page 6, lines 23-29).

Drug Facts and Comparisons teach timolol, a beta-blocker, to be employed to reduce elevated and normal intraocular pressure with or without glaucoma (page 2287).

The mechanism appears to be a reduction of aqueous production, and a slight increase in outflow facility. Regarding claims to regulating salt uptake or release by ciliary epithelial cells of the human eye by modulation of the antiports, this action is considered to be inherent. Applicants' attention is directed to *Ex parte Novitski*, 26 USPQ2d 1389 (BOPA 1993) illustrating anticipation resulting from inherent use, absent a *haec verba* recitation for such utility. In the instant application, as in *Ex parte Novitski*, supra, the claims are directed to preventing a malady or disease with old and well-known compounds or compositions. It is now well-settled law that administering compounds inherently possessing a protective utility anticipates claims directed to such protective use. Arguments that such protective use is not set forth *haec verba* are not probative. Prior use for the same utility clearly anticipates such utility, absent limitations distancing the proffered claims from the inherent anticipated use. Attempts to distance claims from anticipated utilities with specification limitations will not be successful. At page 1391, *Ex parte Novitski*, supra, the Board said "We are mindful that, during the patent examination, pending claims must be interpreted as broadly as their terms reasonably allow. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989). As often stated by the CCPA, "we will not read into claims in pending applications limitations from the specification." *In re Winkhaus*, 52 F.2d 637, 188 USPQ 219 (CCPA 1975)." In the instant application, Applicants' failure to distance the proffered claims from the anticipated **prophylactic** utility renders such claims anticipated by the prior inherent use. Regarding administration of the composition to the ciliary epithelial cells of the aqueous humor, there does not seem to be any description of how one would bypass

administering an eyedrop to an eye to administer said compositions to the ciliary epithelial cells of the aqueous humor. A prior art reference may anticipate without disclosing a feature of the claimed invention, if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991). Other precedents of the court have held that inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. E.g., *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1351 (Fed. Cir. 2002); *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999) ("Where the result is a *necessary consequence* of what was deliberately intended, it is of no import that the article's authors did not appreciate the results."); Atlas Powder, 190 F.3d at 1348-49 ("Because 'sufficient aeration' was inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention. An inherent structure, composition, or function is not necessarily known."). In the instant case, the unappreciated anticipation also does not require recognition. Applicant claims to have discovered the method of modulating aqueous secretion by modulating the antiports of the aqueous humor. Since the pharmaceutical compositions claimed by applicant produced the claimed modulation of aqueous secretion, the discovery of the modulation of the antiport is inherent. In the context of the accidental anticipation, beta-blockers, such as timolol, do not accidentally modulate the antiport when the pharmaceutical composition is applied to a patient in need of treatment. The antiport necessarily and inevitably is modulated

when the beta-blocker is applied and does not require a skilled artisan to recognize the inherent characteristic in the prior art that anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 94-96, 99-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adorante et al. U.S. Patent No. 5,559,151 and Cherksey U.S. Patent No. 4,950,591.

Adorante et al. teach pharmaceutical compositions and methods for treating glaucoma and/or ocular hypertension comprising administering to the mammalian eye an agent such as 4,4'-diisothiocyanatostilbene-2,2'-disulfonate (DIDS) (see column 5, lines 10-18). It is noted that Adorante et al. identifies this agent as a chloride channel blocker. The identification of the agent DIDS as a chloride channel blocker does not detract from the teaching that this agent, when it is administered to the mammalian eye, treats ocular hypertension/glaucoma because the chloride-dependent ion flux pathways will inhibit aqueous humor formation and thus, lower intraocular pressure (IOP) (column 5, lines 45-49). Adorante further teaches that drugs currently utilized in the treatment of glaucoma include, *inter alia*, miotics, sympathomimetics, beta blockers, alpha-2-agonists and carbonic anhydrase inhibitors. In vitro (see example, column 5) and in vivo (see claim 1) use are clearly disclosed.

Adorante et al. fails to teach coadministration of NHE/NHE-1 inhibitors.

Cherksey teaches amiloride (NHE inhibitor/NHE-1 inhibitor) is an agent that selectively blocks ion transport and interacts with a Sodium Hydrogen Exchange inhibitor at high concentrations (column 1, lines 21-27). Amiloride and derivatives are capable of regulating membrane transport, cellular volume or cellular pressure disorders (column 2, lines 5-10). The amiloride derivatives are useful when applied topically for

the treatment of glaucoma (column 3, line 66 to column 4, line 3 and column 5, lines 42-47).

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980):

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in *Crockett*, the idea of combining them flows logically from their having been individually taught in the prior art.

It would have been made obvious to one of ordinary skill in art at the time it was made to employ two agents well-known to treat glaucoma/ocular hypertension together to treat the very same condition. *Adorante et al.* teach that DIDS treats glaucoma and/or ocular hypertension by inhibiting aqueous humor formation and thus, lowering IOP. *Cherksey* teaches amiloride (NHE inhibitor/NHE-1 inhibitor) is an agent that selectively blocks ion transport and interacts with a Sodium Hydrogen Exchange inhibitor at high concentrations (column 1, lines 21-27). Amiloride and derivatives are capable of regulating membrane transport, cellular volume or cellular pressure disorders. One would have been motivated to combine these treatments motivated by the reasoned expectation of producing a composition, which is effective in comprehensively treating persons suffering from elevated intraocular pressure and glaucoma.

Regarding claims drawn to regulating salt uptake or release by ciliary epithelial cells of the human eye or eye of an animal having a trabecular meshwork (network) by

controlling or modulating the function of one or more antiports of the aqueous humor ciliary epithelial cells by administering to the ciliary epithelial cells of the aqueous humor a modulating amount of a pharmaceutical composition consisting essentially of an NHE inhibitor, Applicants' attention is directed to *Ex parte Novitski*, 26 USPQ2d 1389 (BOPA 1993) illustrating anticipation resulting from inherent use, absent a *haec verba* recitation for such utility. In the instant application, as in *Ex parte Novitski*, supra, the claims are directed to preventing a malady or disease with old and well known compounds or compositions. It is now well settled law that administering compounds inherently possessing a protective utility anticipates claims directed to such protective use. Arguments that such protective use is not set forth *haec verba* are not probative. Prior use for the same utility clearly anticipates such utility, absent limitations distancing the proffered claims from the inherent anticipated use. Attempts to distance claims from anticipated utilities with specification limitations will not be successful. At page 1391, *Ex parte Novitski*, supra, the Board said "We are mindful that, during the patent examination, pending claims must be interpreted as broadly as their terms reasonably allow. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989). As often stated by the CCPA, "we will not read into claims in pending applications limitations from the specification." *In re Winkhaus*, 52 F.2d 637, 188 USPQ 219 (CCPA 1975)". In the instant application, Applicants' failure to distance the proffered claims from the anticipated prophylactic utility, renders such claims anticipated by the prior inherent use.

Claims 94-98, 102-113 rejected under 35 U.S.C. 103(a) as being unpatentable over Brandt et al. U.S. Patent No. 5,585,401 and Cherksey U.S. Patent No. 4,950,591.

Brandt et al. teach the administration of compounds that inhibit the function of $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter mechanism (symport) (see abstract) such as bumetanide for topical administration (column 6, lines 30-43). It has been discovered that the trabecular meshwork of the mammalian eye regulate cell volume and fluid transport by means of the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter mechanism. Compounds that substantially inhibit operation of this mechanism also increase the outflow of the ocular fluids, thus lowering intraocular pressure for treatment of ocular hypertension and glaucoma (column 6, lines 15-29).

Brandt et al. fails to teach coadministration of NHE/NHE-1 inhibitors.

Cherksey teaches amiloride (NHE inhibitor/NHE-1 inhibitor) is an agent that selectively blocks ion transport and interacts with a Sodium Hydrogen Exchange inhibitor at high concentrations (column 1, lines 21-27). Amiloride and derivatives are capable of regulating membrane transport, cellular volume or cellular pressure disorders (column 2, lines 5-10). The amiloride derivatives are useful when applied topically for the treatment of glaucoma (column 3, line 66 to column 4, line 3 and column 5, lines 42-47).

As stated in In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980):

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d

442, 445, 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in Crockett, the idea of combining them flows logically from their having been individually taught in the prior art.

It would have been made obvious to one of ordinary skill in art at the time it was made to employ two agents well-known to treat glaucoma/ocular hypertension together to treat the very same condition. Adorante et al. teach that DIDS treats glaucoma and/or ocular hypertension by inhibiting aqueous humor formation and thus, lowering IOP. Cherksey teaches amiloride (NHE inhibitor/NHE-1 inhibitor) is an agent that selectively blocks ion transport and interacts with a Sodium Hydrogen Exchange inhibitor at high concentrations (column 1, lines 21-27). Amiloride and derivatives are capable of regulating membrane transport, cellular volume or cellular pressure disorders. One would have been motivated to combine these treatments motivated by the reasoned expectation of producing a composition which is effective in comprehensively treating persons suffering from elevated intraocular pressure and glaucoma. Regarding administration of the composition to the ciliary epithelial cells of the aqueous humor, there does not seem to be any description of how one would bypass administering an eyedrop to an eye to administer said compositions to the ciliary epithelial cells of the aqueous humor. A prior art reference may anticipate without disclosing a feature of the claimed invention, if that missing characteristic is necessarily present, in the single anticipating reference. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991).

Regarding claims drawn to regulating salt uptake or release by ciliary epithelial cells of the human eye or eye of an animal having a trabecular meshwork (network) by controlling or modulating the function of one or more antiports of the aqueous humor ciliary epithelial cells by administering to the ciliary epithelial cells of the aqueous humor a modulating amount of a pharmaceutical composition consisting essentially of an NHE inhibitor, Applicants' attention is directed to *Ex parte Novitski*, 26 USPQ2d 1389 (BOPA 1993) illustrating anticipation resulting from inherent use, absent a *haec verba* recitation for such utility. In the instant application, as in *Ex parte Novitski*, supra, the claims are directed to preventing a malady or disease with old and well known compounds or compositions. It is now well settled law that administering compounds inherently possessing a protective utility anticipates claims directed to such protective use. Arguments that such protective use is not set forth *haec verba* are not probative. Prior use for the same utility clearly anticipates such utility, absent limitations distancing the proffered claims from the inherent anticipated use. Attempts to distance claims from anticipated utilities with specification limitations will not be successful. At page 1391, *Ex parte Novitski*, supra, the Board said "We are mindful that, during the patent examination, pending claims must be interpreted as broadly as their terms reasonably allow. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989). As often stated by the CCPA, "we will not read into claims in pending applications limitations from the specification." *In re Winkhaus*, 52 F.2d 637, 188 USPQ 219 (CCPA 1975)". In the instant application, Applicants' failure to distance the proffered claims from the anticipated prophylactic utility, renders such claims anticipated by the prior inherent use.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

Response to Arguments

Regarding the 112 1st paragraph rejection over claim 101 for use of the term "a prostaglandin precursor, the rejection is maintained. Applicant asserts that since the specification at paragraph [0016] refers to latanoprost, that applicant is entitled to claim all prostaglandin precursors. Considering the teachings provided in the specification as originally filed, the Examiner finds that Applicants have failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set for the claimed invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicants had possession of the concept of all "precursor prostaglandins". Prostaglandin precursors include essential fatty acids, such as arachidonic acid, linoleic acid, eicosapentanoic acid and dihomogammalinoleic acid. Applicant is entitled to claim latanoprost.

In response to applicants assertion that Cherksey is a narrow patent, the claim elements appear in the prior art in the same configurations, serving the same functions, to achieve the results suggested in prior art. The amiloride derivatives are

useful when applied topically for the treatment of glaucoma (column 3, line 66 to column 4, line 3 and column 5, lines 42-47). It is unclear what the applicant is attempting to establish by the recitation of older art by Civan et al. The references cited are not considered to establish patentability of the instant application even though the reference is older than the reference cited above. Cherksey teaches that amiloride selectively blocks (inhibits) ion transport and interacts with a Sodium Hydrogen Exchange inhibitor at high concentrations (column 1, lines 21-27) and regulate membrane transport, cellular volume or cellular pressure disorders (column 2, lines 5-10). Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

Applicants' reliance on the post filing date reference to allegedly provide evidence of patentability is not persuasive. The determination of obviousness or nonobviousness must be based upon what was known in the art at the time the invention was made. See 35 U.S.C. § 103: "A patent may not be obtained...if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art".

Regarding the Drug Facts and Comparisons, applicant claims that the class of molecules designated as NHE inhibitors did not include timolol or any other beta blocker at the time of the invention. In response, the applicant identifies NHE inhibitors to include beta blockers and in particular, timolol in the instant specification. A prior art

reference may anticipate without disclosing a feature of the claimed invention, if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991). Beta blockers have been used for relief of intraocular pressure since at least 1980 (see Shell et al. U.S. Patent No. 4,281,654). The mere fact that they are not identified as NHE inhibitors does not detract from their actions of lowering intraocular pressure. Other precedents of the court have held that inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. E.g., *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1351 (Fed. Cir. 2002); *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999) ("Where the result is a *necessary consequence* of what was deliberately intended, it is of no import that the article's authors did not appreciate the results."); Atlas Powder, 190 F.3d at 1348-49 ("Because 'sufficient aeration' was inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention. An inherent structure, composition, or function is not necessarily known."). In the instant case, the unappreciated anticipation also does not require recognition. Applicants' allegation that claim 94 does not embrace timolol or any other beta blockers is incorrect. Claim 94 is drawn to regulating intraocular pressure with a composition comprising at least one sodium-hydrogen exchanger (NHE) inhibitor. When the examiner looks to the instant specification to identify what applicant means by NHE inhibitors, Page 6 of Applicant's instant specification identifies NHE inhibitors as beta-blockers (see at least page 6, lines 23-29).

Applicant claims to have discovered the method of modulating aqueous secretion by modulating the antiports of the aqueous humor. Since the pharmaceutical compositions claimed by applicant produced the claimed modulation of aqueous secretion, the discovery of the modulation of the antiport is inherent. In the context of the accidental anticipation, beta-blockers, such as timolol, do not accidentally modulate the antiport when the pharmaceutical composition is applied to a patient in need of treatment. The antiport necessarily and inevitably is modulated when the beta-blocker is applied and does not require a skilled artisan to recognize the inherent characteristic in the prior art that anticipates the claimed invention.

Regarding the rejection of claims 94-96, 99-113 over Adorante and Cherksey, applicant asserts that the rejection teaches away. In response, Adorante et al. teach that DIDS treats glaucoma and/or ocular hypertension by inhibiting aqueous humor formation and thus, lowering IOP. Cherksey teaches amiloride (NHE inhibitor/NHE-1 inhibitor) is an agent that selectively blocks ion transport and interacts with a Sodium Hydrogen Exchange inhibitor at high concentrations (column 1, lines 21-27). Amiloride and derivatives are capable of regulating membrane transport, cellular volume or cellular pressure disorders. One would have been motivated to combine these treatments motivated by the reasoned expectation of producing a composition which is effective in comprehensively treating persons suffering from elevated intraocular pressure and glaucoma. Regarding administration of the composition to the ciliary epithelial cells of the aqueous humor, there does not seem to be any description of how one would bypass administering an eyedrop to an eye to administer said compositions

to the ciliary epithelial cells of the aqueous humor. A prior art reference may anticipate without disclosing a feature of the claimed invention, if that missing characteristic is necessarily present, in the single anticipating reference. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Regarding claims drawn to regulating salt uptake or release by ciliary epithelial cells of the human eye or eye of an animal having a trabecular meshwork (network) by controlling or modulating the function of one or more antiports of the aqueous humor ciliary epithelial cells by administering to the ciliary epithelial cells of the aqueous humor a modulating amount of a pharmaceutical composition consisting essentially of an NHE inhibitor, Applicants' attention is directed to *Ex parte Novitski*, 26 USPQ2d 1389 (BOPA 1993) illustrating anticipation resulting from inherent use, absent a *haec verba* recitation for such utility. In the instant application, as in *Ex parte Novitski*, supra, the claims are directed to preventing a malady or disease with old and well known compounds or compositions. It is now well settled law that administering compounds inherently possessing a protective utility anticipates claims directed to such protective use. Arguments that such protective use is not set forth *haec verba* are not probative. Prior use for the same utility clearly anticipates such utility, absent limitations distancing the proffered claims from the inherent anticipated use.

Regarding the rejection Claims 94-98, 102-113 over Brandt and Cherksey, In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Cherksey teaches amiloride (NHE inhibitor/NHE-1 inhibitor) is an agent that selectively blocks ion transport and interacts with a Sodium Hydrogen Exchange inhibitor at high concentrations (column 1, lines 21-27). Amiloride and derivatives are capable of regulating membrane transport, cellular volume or cellular pressure disorders. One would have been motivated to combine these treatments motivated by the reasoned expectation of producing a composition which is effective in comprehensively treating persons suffering from elevated intraocular pressure and glaucoma. Regarding administration of the composition to the ciliary epithelial cells of the aqueous humor, there does not seem to be any description of how one would bypass administering an eyedrop to an eye to administer said compositions to the ciliary epithelial cells of the aqueous humor. A prior art reference may anticipate without disclosing a feature of the claimed invention, if that missing characteristic is necessarily present, in the single anticipating reference. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991).

Regarding claims drawn to regulating salt uptake or release by ciliary epithelial cells of the human eye or eye of an animal having a trabecular meshwork (network) by controlling or modulating the function of one or more antiports of the aqueous humor

ciliary epithelial cells by administering to the ciliary epithelial cells of the aqueous humor a modulating amount of a pharmaceutical composition consisting essentially of an NHE inhibitor, Applicants' attention is directed to *Ex parte Novitski*, 26 USPQ2d 1389 (BOPA 1993) illustrating anticipation resulting from inherent use, absent a *haec verba* recitation for such utility. In the instant application, as in *Ex parte Novitski*, supra, the claims are directed to preventing a malady or disease with old and well known compounds or compositions. It is now well settled law that administering compounds inherently possessing a protective utility anticipates claims directed to such protective use. Arguments that such protective use is not set forth *haec verba* are not probative. Prior use for the same utility clearly anticipates such utility, absent limitations distancing the proffered claims from the inherent anticipated use.

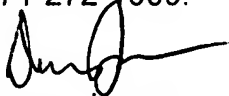
Regarding the Shell reference, Applicant indicates that there are no citations to the reference in the Office action dated July 31, 2007. However, Applicant's attention is drawn to "Response to Declaration" at about page 17 of the office action wherein Shell is cited.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Art Unit 1614

January 6, 2007